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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/889,430	01/17/2002	Mathieu Hubertus Maria Noteborn	2906-4992US	2965

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EXAMINER	
LI, QIAN JANICE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/889,430	NOTEBORN ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-37* is/are pending in the application.

4a) Of the above claim(s) *17,18,27-30 and 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-26,31 and 33-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' amendment and response filed 12/1/03 have been entered. Claims 19, 20, 25, 31, 35 have been amended. Claim 37 is newly added. Claims 19-26, 31, and 33-37 are under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to the specification or pending claims will not be reiterated. The arguments in the response would be addressed to the extent that they apply to current rejections.

This application contains claims (17,18,27-30 and 32) drawn to an invention nonelected without traverse in Paper No. 11. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. § 119 or 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification of in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

WRITTEN DESCRIPTION

Claims 19, 23-25, 31, and 33-35 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Concerning the gene delivery vehicle having a tropism for specific cells or a targeting means, Applicants indicated that the original disclosure recites these terms and the support could be found in the as-filed specification at page 4, lines 7-10 (Remark, page 8, 4th paragraph). However, the recited section of the specification does not even mention targeting means or tissue tropism of a gene delivery vehicle. An adequate written description of the means of targeting requires more than a mere statement that it is part of the invention; what is required is a description of the means itself. It is not sufficient to define DNA solely by its principal biological property, e.g. **a targeting means or a tropism for fibroblast-like synoviocytes**, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any means with that biological property. Also, naming a type of material generically known

to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all means that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). With respect to the method claims, adequate description of the methods first requires an adequate description of the materials, i.e. specific structure or sequence, which provide the means for practicing the invention. The court has made it very clear "CONCEPTION OF CHEMICAL COMPOUND REQUIRES THAT INVENTOR BE ABLE TO DEFINE COMPOUND SO AS TO DISTINGUISH IT FROM OTHER MATERIALS, AND TO DESCRIBE HOW TO OBTAIN IT, RATHER THAN SIMPLY DEFINING IT SOLELY BY ITS PRINCIPAL BIOLOGICAL ACTIVITY". *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). Accordingly, for reasons of record and foregoing, the rejection stands.

To the extent that the claimed invention is not adequately described in the instant disclosure, claims 19, 23-25, 31, and 33-35 also stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been adequately described that is not conventional in the art, and since without such targeting means, the gene

delivery vehicle could not sufficiently reach the target cells if administered from a remote site.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19-26, 31, and 33-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 19 and 20 recite the limitation "said apoptin inducing agent" in line 8. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (f) he did not himself invent the subject matter sought to be patented.

The previous rejections under this section not reiterated here are withdrawn in view of the claim amendment limiting the apoptosis-inducing agent to the protein apoptin, and because none of the reference use apoptin as an apoptosis-inducing agent.

The previous *provisional* rejections not reiterated here are withdrawn because they are filed after the priority date of this application.

Claims 19 and 20 stand rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter. The subject matter as claimed encompasses that of claims 22 and 25 of copending Application No. 09/403,213, and claims 17 and 24 of U.S. patent application 09/764,176, both have a different inventive entity.

Applicants argue that the cited applications are not prior art, and citing MPEP 706.02 (g) arguing that the examiner must presume the applicants are the proper inventors.

In response, the statute set forth in 35 U.S.C. 102(f) does not require an inquiry into the relative dates of a reference (MPEP 2137). Further, applicants only cited the first half of the teaching of the M.P.E.P 706.02 (g), the complete teaching states, "THE EXAMINER MUST PRESUME THE APPLICANTS ARE THE PROPER INVENTORS *UNLESS* THERE IS PROOF THAT ANOTHER MADE THE INVENTION AND THAT APPLICANT DERIVED THE INVENTION FROM THE TRUE INVENTOR". In this case, the cited application claiming the same subject matter is the evidence for the required proof. The court has instructed, although derivation and

priority of invention both focus on inventorship, derivation addresses originality (i.e., who invented the subject matter), whereas priority focuses on which party first invented the subject matter. Price v. Symsek, 988 F.2d 1187, 1190, 26 USPQ2d 1031, 1033 (Fed. Cir. 1993). Thus, 35 U.S.C. 102(f) may apply where 35 U.S.C. 102(a) AND 35 U.S.C. 102(e) are not available statutory grounds for rejection. Accordingly, it is applicant's duty to clarify the record.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 19 and 20 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Sata et al* (PNAS 1998 Feb;95:1213-7), in view of *Zuckermann et al* (US 6,468,986), and applies to claim 26 in view of claim amendment.

Claim 26 specifies that the gene delivery vehicle comprises a recombinant adenovirus. *Sata et al* teach a method comprising administering to injured rat carotid arteries a recombinant adenoviral vector encoding and expressing FasL (an apoptosis-inducing agent), which inhibit the robust T cell infiltration of the vessel wall (e.g. abstract) as discussed in the previous Office action under *35 USC § 102.*

In the Reply, applicants argue that *Sata et al* does not teach or suggest the use of apoptin that exhibits its effects in aberrant cells involved with or related to immune

diseases, and Zuckermann et al when combined with Sata does not remedy the deficiency of Sata because Zuckemann et al teach using apoptin to treat prostate cancer and benign hyperplasia, and does not teach or suggest an apoptosis inducing agent in general.

In response to applicant's argument that no suggestions for combining reference, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In this case, *Sata et al* teach a method comprising administering a recombinant adenoviral vector encoding and expressing FasL (an apoptosis-inducing agent), which inhibit the robust T cell infiltration of the vessel wall (aberrant cells involved with immune disease). *Sata et al* teach that FasL-Fas system has been implicated in the regulation of physiological cell turnover, particularly in the immune system and could be used to alter the T cell response (Introduction), that the inflammatory fibroproliferative disorders of the vessel wall provide a unique system to explore the therapeutic utility of FasL, *Zuckermann et al* listed apoptin *along with* other apoptosis-inducing agents fas, Fas-L, fadd, etc., this is a showing that it is known in the art that apoptin is an *alternative* to Fas-L. *Zuckermann et al* use the term "pro-apoptotic agent", which is an art-known *alternative* to "apoptosis-inducing agent". Thus, *Zuckermann et al* do teach the concept of apoptosis in general and using such for inducing tumor cell death. Here, the

combined teachings of the references would have suggested to those of ordinary skill in the art to modify the methods taught by *Sata et al,* by substituting or combining the apoptin in the gene delivery vehicle as taught by *Zuckermann et al* with a reasonable expectation of success. Note that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See In re O'Farrell, 7 USPQ2d 1673 (CAFC 1988).

Accordingly, for reasons of record and those set forth foregoing, the rejection stands.

Claim 37 is newly rejected under 35 U.S.C. 103(a) as being unpatentable over *Sata et al* (PNAS 1998 Feb;95:1213-7) and *Zuckermann et al* (US 6,468,986) as applied to claims 19, 20, 26 above, and further in view of *Ledley et al* (US 5,792,751).

The combined teachings of *Sata and Zuckermann* teach administering to aberrant cells of a subject a recombinant adenoviral vector encoding apoptin, which have been discussed in detail in the previous Office action, and in the immediate preceding rejection. The combined teachings fail to teach particularly aberrant synoviocyte.

However, before the instant effective filing date, *Ledley et al* teach using gene therapy for treating diseases associated with fluid spaces such as synoviocytes of the joints, particularly using adenoviral vector for efficient transfection of synoviocytes (e.g. column 4, line 65-column 5, line 60), wherein the gene of interest includes an agent that could induce apoptosis (column 24, lines 55-67).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the method taught by *Sata et al and Zuckermann et al* in the process as taught by *Ledley et al* by administering an adenoviral vector encoding and expressing apoptin to the diseased synoviocytes of the inflamed joint with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to do so because it is within the knowledge of the skill to select one of the known apoptosis-inducing agents in the art for suppressing unwanted synovial cell proliferation. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

In the Reply to the previous rejection of Claims 19, 21, and 22 under 35 U.S.C. 103(a) as being unpatentable over *McCormick et al* (US 5,801,029) and *Bujard et al* (US 5,814,618), applicants argue that neither reference alone or in combination teach or suggest each and every element the invention as amended.

In response, the rejection has been modified in view of claim amendment.

Claims 19-22, 26, 36 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over *Sata et al* (PNAS 1998 Feb;95:1213-7) and *Zuckermann et al* (US 6,468,986) as applied to claims 19, 20, 26 above, and further in view of *McCormick et al* (US 5,801,029), and *Bujard et al* (US 5,814,618).

The combined teachings of *Sata and Zuckermann* teach administering to aberrant cells of a subject a recombinant adenoviral vector encoding apoptin and

transfecting aberrant cells associated with inflammation with such vector, which have been discussed in detail in the previous Office action and foregoing. The combined teachings fail to teach using a suicide gene and an inducible promoter in the gene delivery vehicle.

McCormick et al teach a method comprising administering to a subject mutant viruses (an apoptosis-inducing agent), which preferentially replicate in neoplastic cells and inducing apoptotic cell death in these cells (abstract and column 6, lines 11-13). *McCormick et al* goes on to teach that the virus is adenovirus optionally expressing a cytopatheic gene e.g. HSV tk (suicide gene, column 3, lines 21-25 and paragraph bridging columns 14 and 15). *McCormick et al* do not particularly teach that the tk gene is expressed in an inducible manner.

Bujard et al teach an inducible promoter system (abstract) that could be used for regulating gene expression, such as TK gene, so that the suicide gene could be expressed in a controlled manner and the inducible promoter adds safety to the use of a suicide gene (column 39, lines 57-66).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the methods taught by *Sata et al, Bujard et al* with that of *McCormick et al and Bujard et al* by including a suicide gene e.g. TK in the Adv-apoptin vector construct and using an inducible promoter for controlling the expression of the suicide gene with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to make the modification because the suicide gene could augment the cell death effect induced by apoptin and the inducible promoter

adds to the general safety and usefulness of the suicide gene. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 19 and 20 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 22 and 25 of copending Application No. 09/403,213, for reasons of record and because the amended claims 22 and 25 of the cited application are drawn to delivery the nucleic acid of VP3, which is an alternate name for apoptin.

Applicants indicate that if any issues remain, upon an indication of allowable subject matter, the issue will be dealt with then.

In response, until the issue is dealt with, the rejection stands for reasons of record and foregoing.

Claims 19 and 20 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 17 and 24 of copending Application No. 09/764,176, now allowed. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the present application and that of the cited patent application are each drawn to a method comprising administering to a subject a gene delivery vehicle expressing an apoptosis inducing agent exhibiting its effect in aberrant cells, wherein the agent is apoptin or derivative.

Applicants indicate that if any issues remain, upon an indication of allowable subject matter, the issue will be dealt with then.

In response, until the issue is dealt with, the rejection stands for reasons of record and foregoing.

The prior provisional rejection of claims 19 and 20 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 15 and 19 of copending Application No. 09/819,308 is withdrawn in view of the claim amendments of the cited patent application, no longer drawn to apoptin.

The prior provisional rejection of claims 19 and 20 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 27 and 28 of copending Application No. 09/733,416 is withdrawn in view of the election of

invention in the cited application, wherein claims 27 and 28 are drawn to non-elected invention.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Amy Nelson** can be reached on 571-272-0804. The fax numbers for the organization where this application or proceeding is assigned are **703-872-9306**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is **703-308-0196**.

JANICE LI
PATENT EXAMINER

Q. Janice Li
Patent Examiner
Art Unit 1632

QJL
March 7, 2004